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EXAMINER	
SINGH, ANOOP KUMAR	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 04/04/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/643,233	LOBEL ET AL.	
	Examiner	Art Unit	
	Anoop Singh	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *17-19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *8/18/2003*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-16 and 20-30 have been cancelled by amendment filed on August 18, 2003.

2. Claims 17-19 are pending.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 17-19 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In determining whether Applicant's claims are enabled, it must be found that one of skill in the art at the time of invention by applicant would not have had to perform "undue experimentation" to make and/or use the invention claimed. Such a determination is not a simple factual consideration, but is a conclusion reached by weighing at least eight factors as set forth in In re Wands, 858 F.2d at 737, 8 USPQ

1400, 2d at 1404. Such factors are: (1) The breadth of the claims; (2) The nature of the invention; (3) The state of the art; (4) The level of one of ordinary skill in the art; (5) The level of predictability in the art; (6) The amount of direction and guidance provided by Applicant; (7) The existence of working examples; and (8) The quantity of experimentation needed to make and/or use the invention.

These factors will be analyzed, in turn, to demonstrate that one of ordinary skill in the art would have had to perform "undue experimentation" to make and/or use the invention and therefore, applicant's claims are not enabled.

Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working example are not disclosed in the specification, therefore enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of the invention, therefore, skepticism raised in enablement rejections are those raised in the art by artisan of expertise.

Claim 17 is drawn to a method for treating late infantile neuronal ceroid lipofuscinosis (LINCL) by increasing the levels of CLN2 in cells of an animal. Claim 18 limits the increasing level of CLN2 to include administration of CLN2 to the animal. Subsequent claim limits the increasing the level of CLN2 of claim 18 to include a recombinant vector to the affected cell wherein expression vector provides expression of the CLN2 *in vivo*.

The aspects considered broad are: the breadth of subject population, any method of administration to affect a neurodegenerative disease, any method of increasing the level of CLN2 subsequently limiting to administering a vector comprising

nucleic acid encoding CLN2 and increasing the levels of CLN2 in any cell to treat LINCL (a neuro-degenerative disease).

It is noted that as recited, claimed invention reads on a broad genera of gene and protein therapy. Specific considerations for *in vivo* protein and gene therapeutic transfer such as fate of the protein or DNA vector itself (e.g. volume of distribution, rate of clearance into tissue) and consequences of altered gene expression and protein production, have to be addressed for an *in vivo* protein or gene therapy method of treating LINCL in an animal. Additionally, considerations for gene transfer include selection of a vector system for sufficient term expression of the therapeutic protein and regulation of its expression in target cells. Although Applicant's specification teaches role of CLN2 in progression of LINCL, the specification fails to provide an enabling disclosure for the claimed invention because the specification fails to provide sufficient guidance as to (i) how an artisan of skill would have practiced the claimed method in any animal, (ii) the claimed method would have resulted in providing the CLN2 in deficient cells in amount sufficient to treat any LINCL disorder caused by the deficiency of CLN2 by administering CLN2 or nucleic acid encoding CLN2 protein to any site. An artisan would have to carry out extensive experimentation to practice the invention, and such experimentation would have been undue because art of gene/ protein therapy and gene delivery *in vivo* is unpredictable and specification fails to provide any guidance as to how the claimed method would have been practiced in animals. As will be shown below, these broad aspects as well as limitations were not enabled for the claimed invention at the time of filing of this application because neither

the specification nor the art of record taught sufficient guidance to practice the claimed invention. For purposes to be shown in the state of the prior art, the question of lack of enablement is discussed.

The specification teaches that the invention relates to LINCL-associated gene CLN2 and gene product and methods for diagnosing and treating LINCL (pp 2-4). Pages 5-9 broadly summarize the invention and provide a brief description of figures. Pages 10-43 provide a detailed description of preferred embodiments, definition of terms, antibodies of CLN2, detection of CLN2 and therapeutic aspects of CLN2. Pages 44-46 describe therapeutic aspect of LINCL by delivering CLN2 for the treatment.

However, such broad disclosure does not demonstrate the information required by the Artisan to reasonably predict that any protein or transgene can be expressed in at any cell of any animal at therapeutic effective levels. The art of protein and gene therapy and their delivery at the time of the filing of this application was unpredictable wherein any gene was expressed in an individual suffering from CNS disorder.

While progress has been made in recent years for *in vivo* gene transfer, vector targeting *in vivo* to be desired organs continued to be unpredictable and inefficient. For example, numerous factors complicate the gene delivery art that cannot be overcome by routine experimentation. These include, the fate of DNA vector itself, volume of distribution, rate of clearance in tissue, the in vivo consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of RNA produced, the amount and stability of the

protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced. These factors differ significantly based on the vector used and the protein being produced (Goodman & Gilman's The Pharmacological basis of Therapeutics, McGraw-Hill, New York, NY. pp 77-101).

Given this lack of reasonable predictability in Applicant's specification and the art, the Artisan would require a large amount of information from Applicant's examples to provide the guidance to provide reasonable predictability.

Applicant's examples describe isolation, identification and characterization of CLN2 and corresponding gene product (pp 47-49). It is noted that specification teaches the role of CLN2 in LINCL (example 2) in patients, however specification fails to describe any therapeutic benefit by delivering nucleic acid encoding CLN2 protein to any cells.

At the time of filing, gene therapy utilizing the direct administration of recombinant nucleic acids, whether in the form of retroviruses, adenoviruses or plasmid DNA/liposome complexes, was considered highly unpredictable. Verma et al states that, "[t]he Achilles heel of gene therapy is gene delivery...", and that, "most of the approaches suffer from poor efficiency of delivery and transient expression of the gene " (Verma et al, 1997, Nature, 389, pp 239, col. 3, para 2). Marshall (Science, 1995; 269, 1050,1052-55) concurs, stating that" difficulties in getting genes transferred efficiently to target cells and getting them expressed-remains a nagging problem for the entire field", and that many problem must be solved before gene therapy will be useful for

more than the rare application" (Marshall, 1995, 269, pp 1054, col. 3, para 2 and pp 1055, col. 1).

The specification does not disclose the effectiveness of the method of the instant invention in treating LINCL. Nor does it teach the effectiveness of the method in increasing the level of CLN2 in any cell and reversal of any pathology associated with LINCL. The specification only teaches role of CLN2 in progression of LINCL, but fails to disclose any method in treating LINCL. In summary, specification as filed does not teach how nucleic acid encoding CLN2 administered via any route to any mammal could transduce any cells such that any active CLN2 is translated. Furthermore, It is noted that the specification does not provide any guidance as to how much vector should to be delivered for transduction of cells in organ of any animal that would be adequate for therapeutic response. The method of gene therapy and gene delivery in a animal specifically in humans was not routine, rather was unpredictable at the time of filing of this application as neither art of record nor the specification teaches how to practice the claimed inventions.

The method disclosed in specification does not provide any specific guidance that sustained expression of any gene could be achieved by administering transgene by any route to any cell. Furthermore, the state of the prior art effectively summarized by the reference of Carter et al (British Journal of Psychiatric, 2001, 178: 392-394) while reviewing the state of gene therapy in CNS conclude, "Advances in gene transfer technologies now provide an array of versatile tolls for gene delivery to localized or wide spread area of the brain. However, the optimism generated by the results in animal

models must be tempered because many improvements in safety, efficacy, stability and regulation of gene transfer are required before clinically effective gene therapy can be accomplished in human patient." Carter et al further state that gene therapy attempts in organs with greater accessibility than brain have so far met with disappointing outcome, suggesting that at the time of filing of this application gene therapy strategies in treating CNS disorder was limited to preclinical animal models with some potential to make CNS gene therapy an achievable goal in humans (pp393, last paragraph). Furthermore, in spite of greater flexibility with AAV vectors and its usefulness in physiological research, Shevtsova et al (2005) in a post filing art emphasized that selecting a right vector with an appropriate combination of promoters and serotypes remains an important issue to consider for any gene therapy (pp 58, left column, 2nd paragraph).

Next, it is noted that because the mechanism of development of each disease is different, the parameters of treating any particular LSD (providing the cell with active enzyme), will be different, from those used in treating another disease such as LINCL and therefore, the reversal of the symptoms in one case due to gene therapy can not be predictive of the effects in another. Such parameters will include the site of action of the enzyme, cell types and tissues affected by the enzyme deficiency (Schuchman EH, Chemistry and Physics of lipids 102: 179-188, 1999; pp 187 left column, 2nd paragraph). Therefore, the strategy for administering any one enzyme for the treatment will be determined by consideration of cell type, mode of action of enzyme and the organs affected and will be critically different from those from another enzyme and an artisan could not rely on the results obtained in animal model of one disease to extrapolate to

any other disease model. Barranger et al (Neurochemical Research, 1999, 24, 601-615), while reviewing the state of the art of gene transfer approaches to the lysosomal storage disease, summarized some of the unpredictability issues associated with the treatment method of lysosomal enzyme deficiency diseases. "The approaches and results present in this paper indicate that gene transfer as a therapy for lysosomal storage disorder requires a significant amount of laboratory and clinical investigation. A variety of studies employing several different systems will be necessary to decide which of the approaches will be effective for these disorders, each of which has its own unique characteristics and complications". The specification does not provide any specific guidance how CLN2 could be delivered to an animal such that enough of CLN2 is made for appropriate time for the treatment of LINCL.

The specification also contemplates using cationic liposome of delivering CLN2 to the target cell. However, there are art-recognized limitations of using cationic liposome for DNA delivery *in vivo* and there is no teaching or contemplation as to how an artisan of skill would have addressed these limitations. For example, Filion et al (Br J Pharmacol. 1997;122(3): 551-557) listed several adverse effects associated with cationic lipids or cationic liposome (table 2, pp 18) such as immunomodulation of animals, complement activation, induction of pulmonary inflammation and toxicity. The specification does not provide any guidance as to what doses of the cationic lipid would be used in the method without eliciting adverse effects. It is noted that the prior art at the time of filing of this application did not provide any guidance in this regard either.

Davis et al (Current Opinion in Biotechnology 2002, 13:128–131) evinces an optimistic outlook for non-viral delivery system but states "perfect system does not currently exist". Davis et al describe problems associated with non-viral gene delivery system, which includes obstacles in manufacturing, toxicity, formulation and stability.

With regards to evaluation of efficacy of a therapeutic protein, dosing, clearance and efficacy of the product, preclinical evaluation for toxicity and immunogenicity are important steps. It is noted that toxicity with proteins often presents differently that with small-molecule pharmaceutical drugs (Scientific Considerations Related to Developing Follow-On Protein Products, 2004, p. 4, paragraph 1). Further, immunogenic responses in patients can be triggered by large-molecules products, product-related or process-related impurities raising unwanted antibodies. Additionally, the way in which unwanted immunogenicity may present in different patients is unpredictable and varied, even with identical amino acid sequences; immunogenicity to the product can vary dramatically (Scientific Considerations Related to Dèveloping Follow-On Protein Products, 2004, p. 5, paragraph 1). Thus, preclinical evaluation for efficacy and immunogenicity of a therapeutic protein is vital for the development of therapeutic protein. In the earlier phase of testing, it is important to assess the half-life and clearance of the protein as the terminal elimination half-life of related products can vary drastically. For example, six companies manufacture FDA-approved versions of human growth hormone, with the same number of amino acid and very similar molecular weights, presented terminal half-life from 1.75 to 10 hours. Thus, such large variations can impact the effectiveness of the product and the as the body's immune response to

it (Scientific Considerations Related to Developing Follow-On Protein Products, 2004, p. 5, paragraph 1). Hence, the risk of immunogenicity should be assessed for each product and characterized with appropriate therapeutic response.

Next, Cooper J (Curr Opin Neurol. 2003, 16(2): 121-8) in a post filing art states, [a]t present, the therapeutic outlook for the NCLs remains bleak, and many ethical and technical challenges remain to be surmounted. ... Suitable models do not yet exist for all forms of NCL. Cooper et al evinces an optimistic outlook for replacement of the missing enzyme that may be an option, in NCL and LINCL, but notes... [p]roblems of enzyme production and the method of delivery will need to be overcome. Moreover, absence of immunogenicity in an animal does not ensure that immunogenicity will not present later in humans (Scientific Considerations Related to Developing Follow-On Protein Products, 2004, p. 5, paragraph 2). Thus, the relevance of animal models for regulation of the immune response in humans may be compromised by phenotypical difference between human patient and animal models of the disease, in particular when the disorder is not the result of a single gene product as in the case of LINCL that is manifested by different mutations of CLNs (1-8). Thus, the state of prior art teaches a lack of nexus between the treatment of an animal *in vivo* with the production of a therapeutic effect comprising the administration of the gene or protein or its variants. Hence, one skill in the Art at the time of the invention could not reasonably predict that the use of CLN2 for protein or gene therapy will treat LINCL in any animal.

In relation to the use of any type of vector to express the nucleic acid encoding a CLN2. Applicants contemplate the use of a variety the vectors including retrovirus,

adenovirus, adeno-associated virus. Prior art teaches the challenging issues faced in the applications of vectors for gene therapy and the need to use of a gene delivery system that is efficient, safe, non-immunogenic and allows for short or long-term protein expression as required by the clinical target. A reasonable correlation must exist between the scope of the claims and scope of enablement set forth in the specification as filed. Without sufficient guidance, the mere enumeration of a number of vectors to highly express a nucleic acid encoding CLN2 for the treatment of LINCL in any animal is unpredictable and the experimentation left to those skilled in the art is unnecessarily and improperly extensive and undue.

With regards to evaluation of a therapeutic protein, dosing, clearance and efficacy of the product, Prior art teaches that preclinical evaluation for immunogenicity are important steps. The specification contemplates administration of a CLN2 in a manner that increases the level of CLN2 by direct administration of the construct (p. 40 line 30), however, the specification fails to teach any immunogenicity or adverse reaction in the animal as a result of said administration. Hence, one skill in the Art at the time of the invention could not reasonably predict that the use of CLN2 for protein therapy will treat LINCL in an animal.

In conclusion, in view of breadth of the claims and absence of a strong showing by Applicant, in the way of specific guidance and direction, and/or working examples demonstrating the same, such invention as claimed by Applicant is not enabled for the claimed inventions. The specification and prior art do not teach a method of *in vivo* delivery of CLN2 such that it transduces cells sufficiently to elicit a pharmacological

response for a desired duration in the brain of subject suffering from LINCL. An artisan of skill would have required undue experimentation to practice the method as claimed because the art of gene and protein therapy and *in vivo* delivery and treatment of any neurodegenerative condition in general by gene and protein delivery *in vivo* was unpredictable at the time of filing of this application as supported by the observations in the art record.

5. Claims 17-19 are also rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 17 is drawn to a method for treating late infantile neuronal ceroid lipofuscinosis (LINCL) by in creasing the levels of CLN2 in cells of an animal. Claim 18 limits the increasing level of CLN2 to include administration of CLN2 to the animal. Claim 19 limits the increasing the level of CLN2 of claim 18 to include a recombinant vector to the affected cell wherein expression vector provides expression of the CLN2 *in vivo*. In analyzing whether the written description requirement is met for the genus claim, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics, specific features and functional attributes that would distinguish different members of the claimed genus.

The specification describes complete structure nucleic acid and amino acid sequence of human CLN2 in one species. There is no disclosure of any particular structure to function/activity relationship in the single disclosed species. The specification does not provide any disclosure as to what would have been the required structure in various species of mammals or how does it vary. The specification also fails to disclose additional representative species of CLN2 nucleic acid and amino acid sequence by any identifying structural characteristics or properties.

The specification does not provide any disclosure as to what would have been the structure of the representative number of the species of the claimed broad genus as disclosed in specification. The skilled artisan cannot envision the detailed structure of other nucleic acid and amino acid sequence of CLN2 in different species that must show the contemplated biological activity, and therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity/simplicity of the structure and/or methods disclosed in specification.

In conclusion, this limited information is not deemed sufficient to reasonably convey one skilled in art that Applicant was in possession of the claimed broad genus at the time the application was filed. Thus, it is concluded that the written description requirement is not satisfied for the claimed broad inventions.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 17-19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 17 is unclear because it recites an acronym LINCL. Using late infantile neuronal ceroid lipofuscinosis instead of LINCL will obviate this rejection. Claim 18 depends on claims 17.

Claim 19 recites the limitation "affected cell" in the claim. There is insufficient antecedent basis for this limitation in the claim. It is not apparent administration of recombinant expression vector is directed to which affected cell. The instant claim is also vague and indefinite, as it does not set forth any condition that has affected any cells.

Claim 17 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. In this case, there are no active steps in the method claims; the omitted steps are ones that are specific method of administering CLN2. Claim 18 depends on claims 17.

8. No Claims allowed.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anoop Singh whose telephone number is (571) 272-

3306. The examiner can normally be reached on 8:30AM-5:00PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272- 0735. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Anoop Singh, Ph.D.
Examiner, AU 1632

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SUPERVISORY PATENT EXAMINER